Polarized human embryonic stem cell-derived retinal pigment epithelial cell monolayers have higher resistance to oxidative stress-induced cell death than nonpolarized cultures.

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Public Summary:

Age-related macular degeneration (AMD) is a leading cause of blindness in the elderly. In geographic atrophy, the late stage of the prevalent and untreatable dry form of AMD there is cell damage and cell death of the retinal pigment epithelium (RPE), a monolayer of cells immediately external to the light sensitive photoreceptors at the back of the eye. Since a major function of the RPE is to support function of the photoreceptors, loss of RPE leads to further degeneration of the photoreceptors and progressive blindness. Clinical trials are ongoing and are being planned for the use of embryonic stem cell derived RPE for the treatment of AMD. Trials are being designed using either subretinal injection of cell suspensions of stem cell-derived RPE or implantation of patches of monolayers of stem cell-derived RPE grown on a substrate. We have found in animal models of retinal degeneration that RPE cell patches (sheets) survive better than cell suspensions and hypothesized that cell sheets were more resistant to oxidant stress; one of the molecular pathways that have been implication in AMD. Hsiung et al found that sheets of polarized RPE in cell culture were much more resistant to oxidant stress than cell suspensions and evaluated the molecular mechanism of this effect. They found that polarized monolayers of stem cell-derived RPE had higher levels of anti-oxidant enzymes and expressed molecules that favored cell survival when compared with cell suspensions. The authors conclude that resistance to oxidant stress could be a factor in favor of using cell sheets rather than cell suspensions for the treatment of AMD.

Scientific Abstract:

Oxidative stress-mediated injury to the retinal pigment epithelium (RPE) is a major factor involved in the pathogenesis of age-related macular degeneration (AMD), the leading cause of blindness in the elderly. Human embryonic stem cell (hESC)-derived RPE cells are currently being evaluated for their potential for cell therapy in AMD patients through subretinal injection of cells in suspension and subretinal placement as a polarized monolayer. To gain an understanding of how transplanted RPE cells will respond to the highly oxidatively stressed environment of an AMD patient eye, we compared the survival of polarized and nonpolarized RPE cultures following oxidative stress treatment. Polarized, nonpolarized/confluent, nonpolarized/subconfluent hESC-RPE cells were treated with H_2O_2. Terminal deoxynucleotidyl transferase dUTP nick end labeling stains revealed the highest amount of cell death in subconfluent hESC-RPE cells and little cell death in polarized hESC-RPE cells with H_2O_2 treatment. There were higher levels of proapoptotic factors (phosphorylated p38, phosphorylated c-Jun NH_2-terminal kinase, Bax, and cleaved caspase 3 fragments) in treated nonpolarized RPE-particularly subconfluent cells-relative to polarized cells. On the other hand, polarized RPE cells had constitutively higher levels of cell survival and antiapoptotic signaling factors such as p-Akt and Bcl-2, as well as antioxidants superoxide dismutase 1 and catalase relative to nonpolarized cells, that possibly contributed to polarized cells' higher tolerance to oxidative stress compared with nonpolarized RPE cells. Subconfluent cells were particularly sensitive to oxidative stress-induced apoptosis. These results suggest that implantation of polarized hESC-RPE monolayers for treating AMD patients with geographic atrophy should have better survival than injections of hESC-RPE cells in suspension.

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